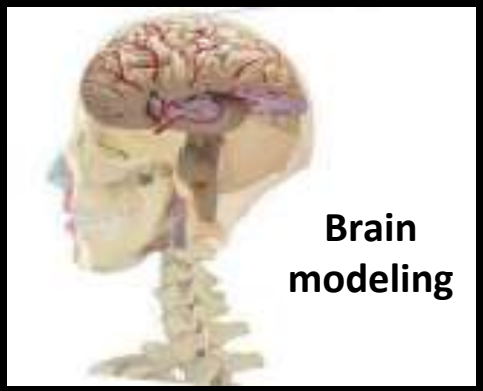
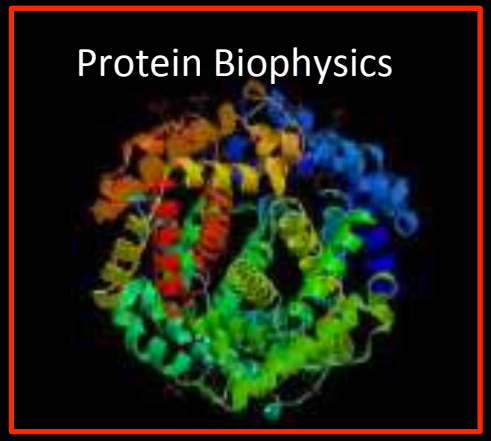
Success stories and practical considerations using HPC resources in academic and industrial use cases

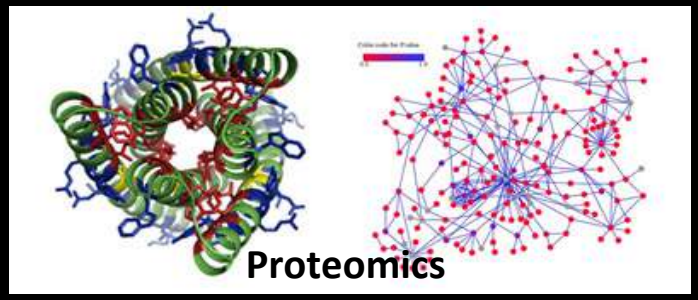
Zoe Cournia
zcournia@bioacademy.gr

EuroCC Greece Workshop - 17 Ιουνίου 2021

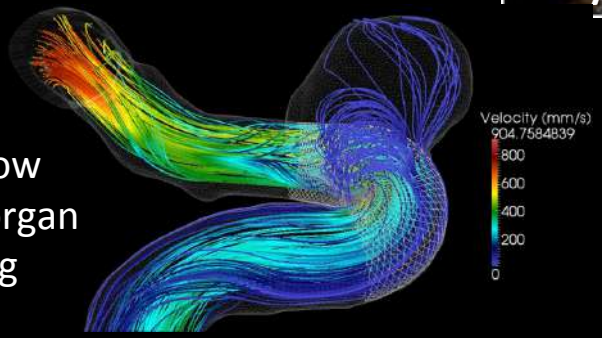
Key areas of biomedical research where HPC is key

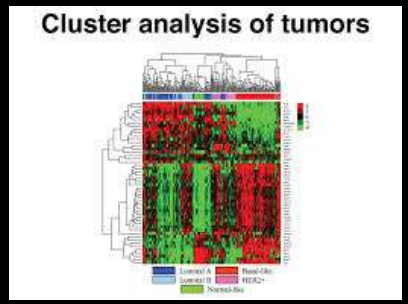






Blood flow
Whole organ
modeling

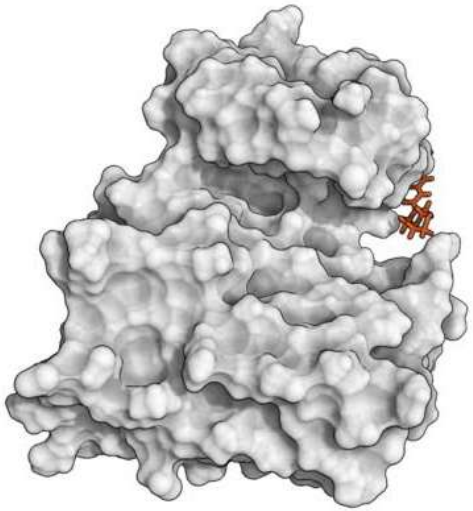


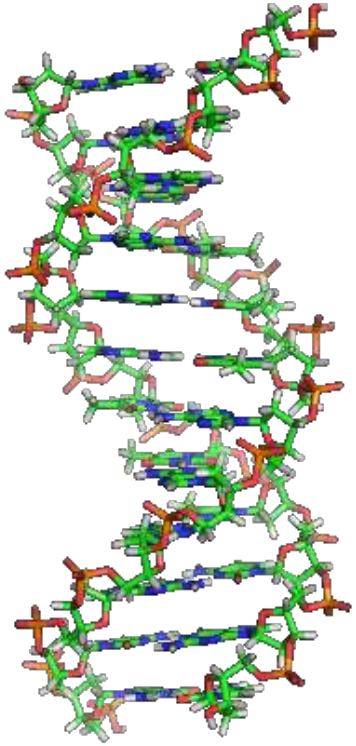


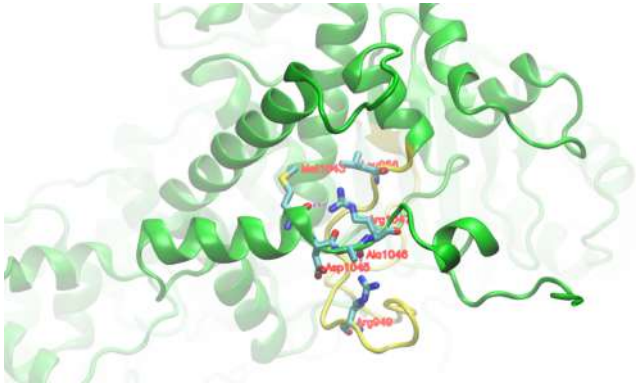
Computational Drug Design

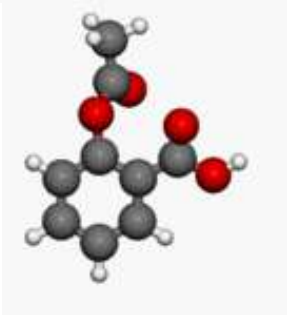
Cournia Lab

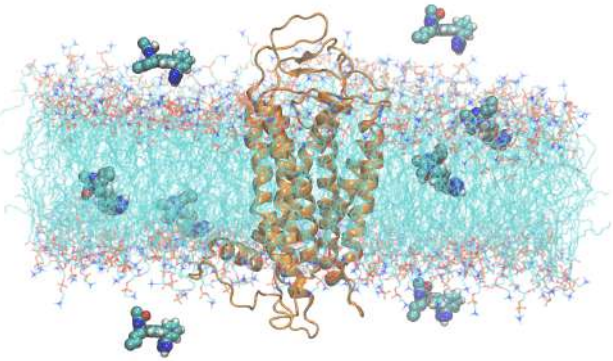
IIBEAA
ΙΔΡΥΜΑ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ
ΑΚΑΔΗΜΙΑΣ ΑΘΗΝΩΝ







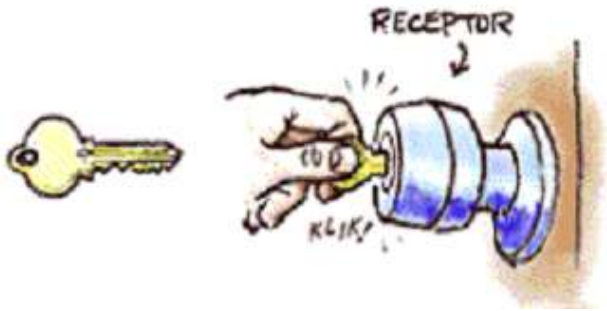


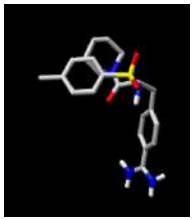


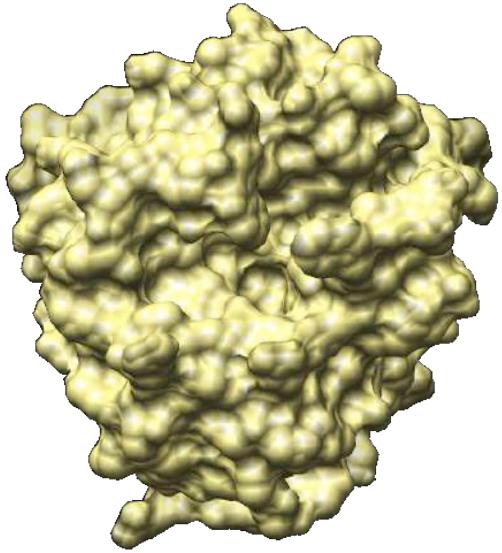
Rational Drug Discovery

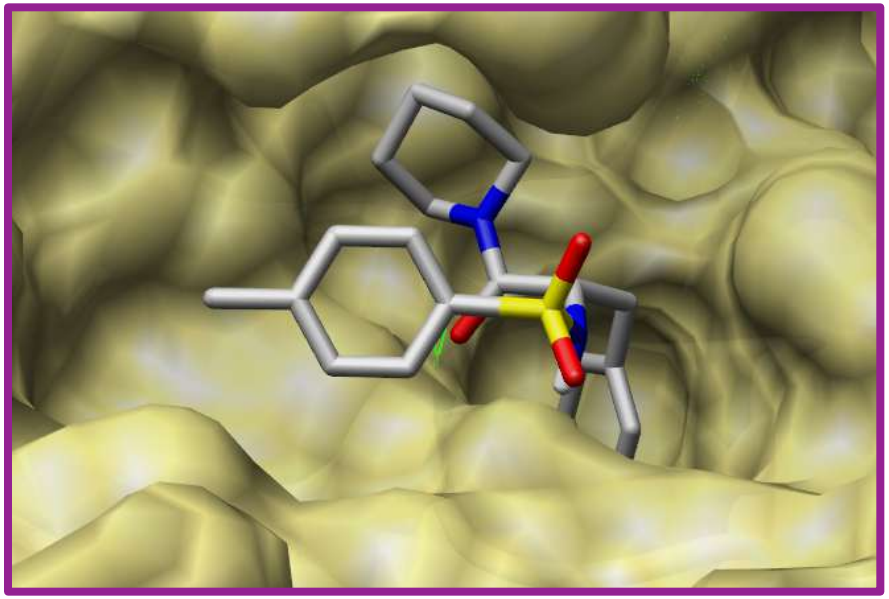
- **Identify important genes for a diseases**
- **Targeting/inactivating genes (proteins) of the pathogen with small molecules = drugs**

TARGETED THERAPY!



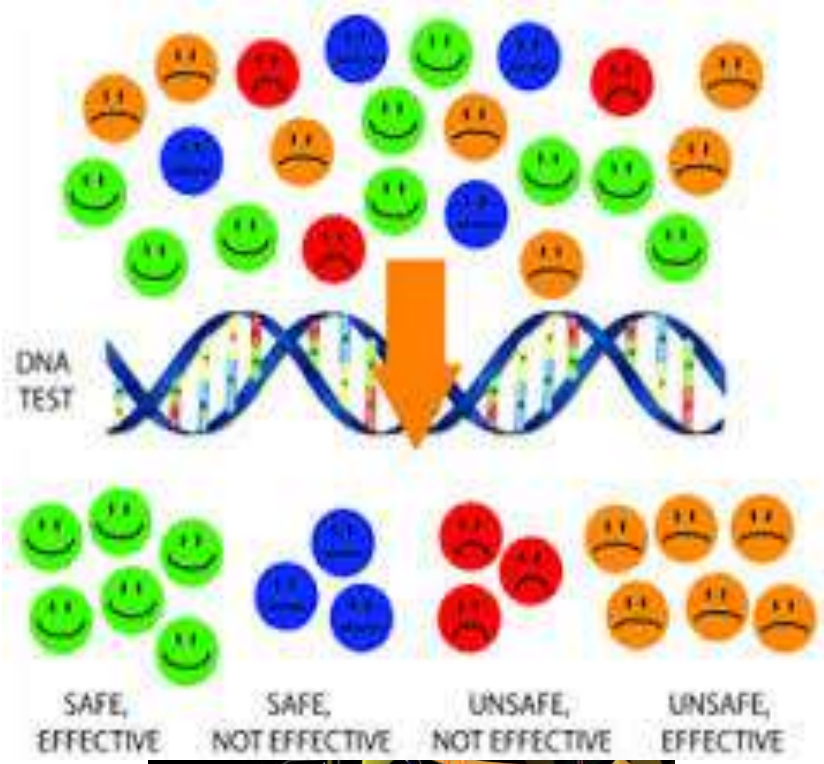






Curr Opin Drug Discov Devel. 2002 May; 5(3): 355–360

The era of Personalized Medicine



Lung Cancer

↓

genotyping

↓

4% of patients with
non-small cell lung carcinoma
Rearrangement in **ALK protein**

↓

carcinogenesis

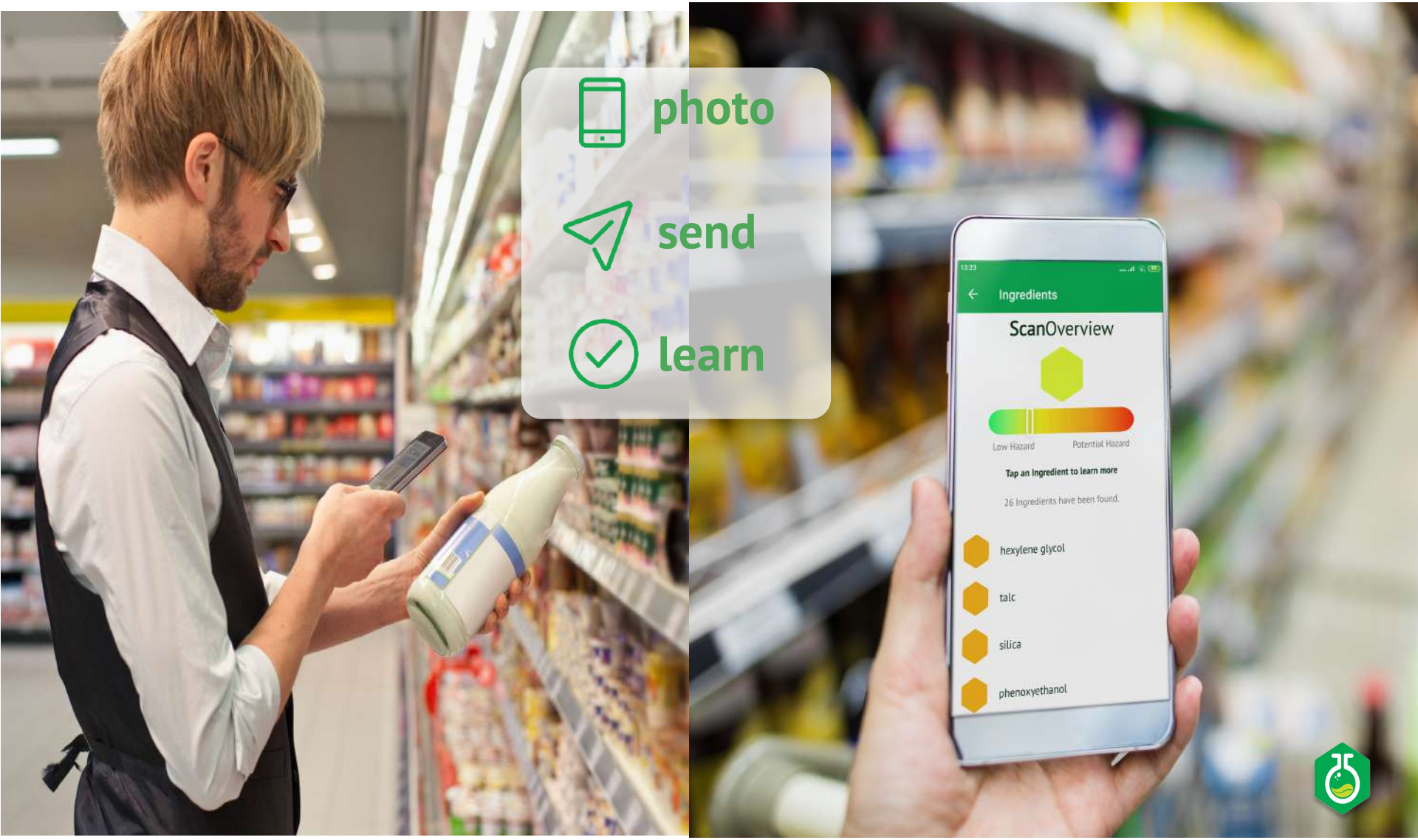
↓

Drug design for this specific
subset of patients

↓

Crizotinib for ALK+
lung cancer patients

Ingredio is an app that makes ingredients easy to understand



Information sourced from institutional databases

European Commission

CosIng COSMETIC INGREDIENTS & SUBSTANCES

NATIONAL INSTITUTES OF HEALTH

PubChem

Unique proprietary scientific algorithms & scoring function

My early days: HP-SEE (2010-2012)

Existing infrastructure – Blue Gene/P

HP-SEE
High-Performance Computing Infrastructure for South East Europe's Research Communities

- IBM Blue Gene/P –**two racks** 2048 *PowerPC 450processors (32 bits, 850 MHz), a total of* ***8192 cores***
- Double-precision, dual pipe floating-point acceleration on each core;
- A total of **4 TB** random access memory;
- 16 I/O nodes currently connected via fiber optics to 10 Gb/s Ethernet switch;
- Theoretical peak performance: Rpeak= **27.85 Tflops;**
- **Energy efficiency: 371.67 MFlops/W Green top 10**

- Smaller HPC machines in **Romania Bulgaria Hungary**
- Upcoming purchases in **Hungary Serbia** and **Greece**

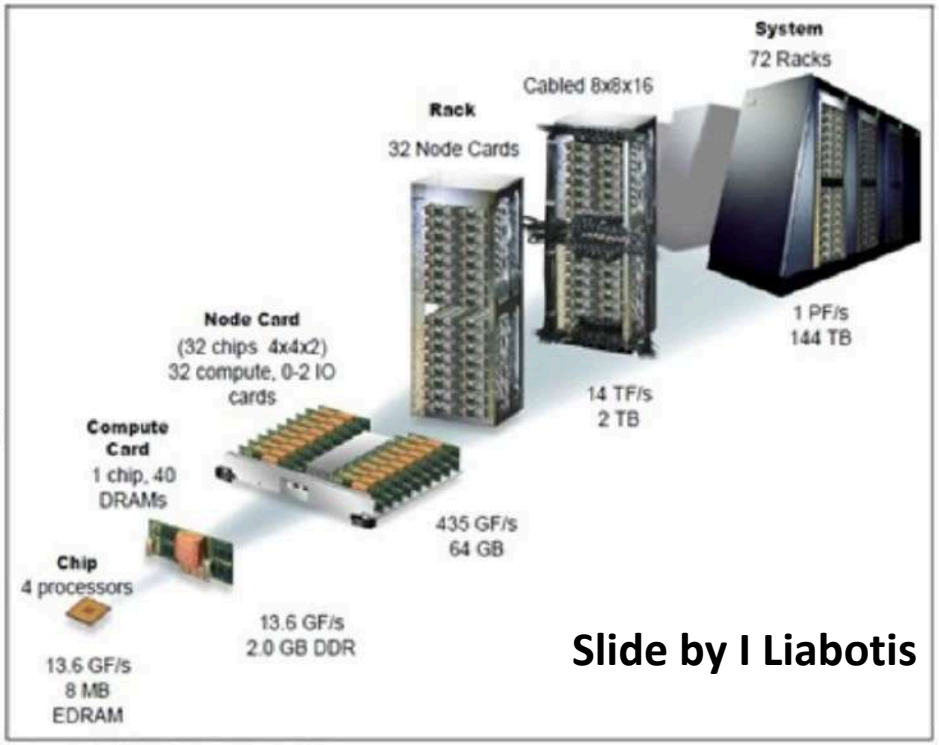


Figure 1-2 Blue Gene/P packaging

Slide by I Liabotis

Key: Getting Preparatory Access

	sec/step			
	CURIE		JUGENE	
cores	NAMD	GROMACS	NAMD	GROMACS
32	0.46	0.096	0.411	0.910
64	0.26	0.05	0.405	0.440
128	0.133	0.027	0.406	0.400
256	0.072	0.014	0.215	0.270
512	0.041	0.008	0.115	0.190
1024	0.023	0.134	0.069	0.140
2048	0.017	0.004	0.047	0.020
4096	-	0.0047	0.045	0.016
8192	-	0.0038	0.042	0.020

Table 1: Results from the benchmark analysis performed on the CURIE and JUGENE clusters

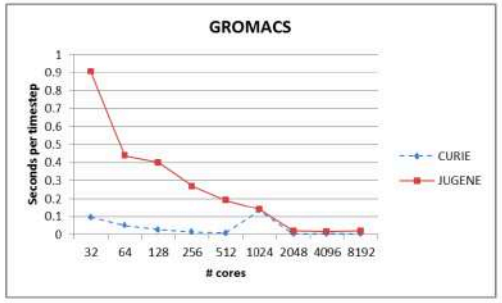


Figure 1: GROMACS performance in CURIE and JUGENE clusters.

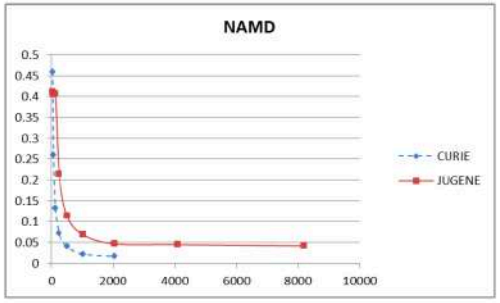
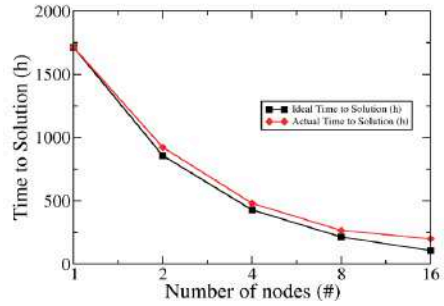
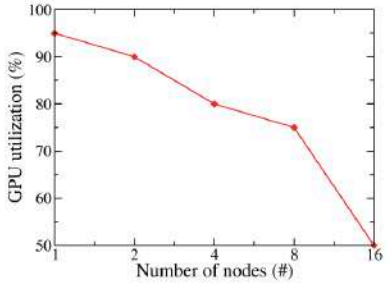


Figure 2: NAMD performance in CURIE and JUGENE clusters.





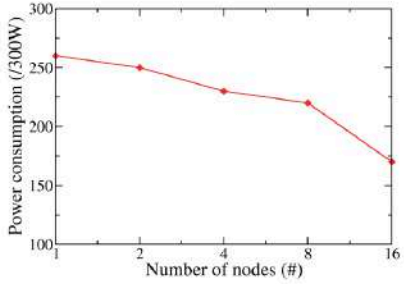
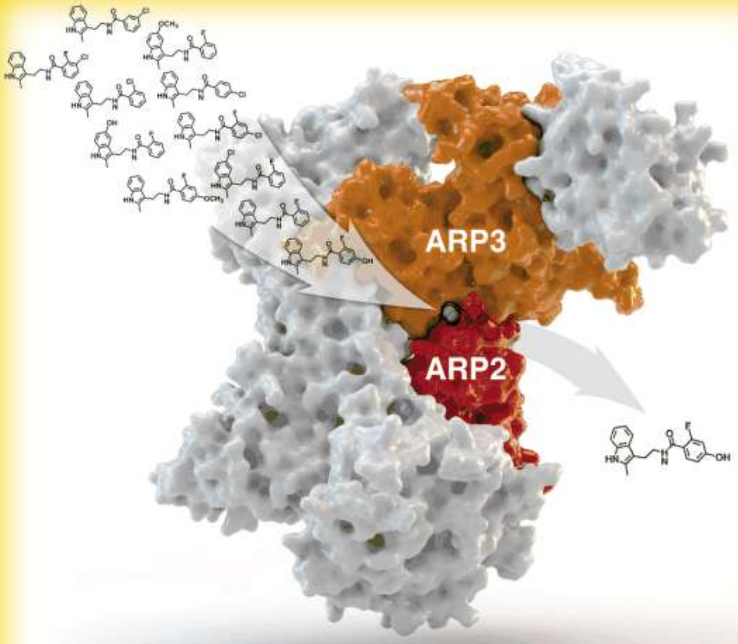


Figure 7. Scaling of multinode NAMD on Marconi100 for 1.3M K-Ras system.

CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY



7/2012

A Journal of ChemPubSoc Europe

The inside cover picture shows the optimization of a small-molecule inhibitor of Arp2/3 complex, a seven-subunit 225 kD protein that nucleates branched actin filaments. The X-ray structure of the complex bound to a known inhibitor, CK-666, was solved, and computational, synthetic, and biochemical methods were used to generate a novel inhibitor with improved potency—an important tool compound for dissecting the cellular functions of Arp2/3 complex. For more details, see the Full Paper by Brad J. Nolen et al. on p. 1286 ff.

www.chemmedchem.org

WILEY-VCH

JCTC Journal of Chemical Theory and Computation

Article

pubs.acs.org/JCTC

Free Energy Calculations Reveal the Origin of Binding Preference for Aminoadamantane Blockers of Influenza A/M2TM Pore

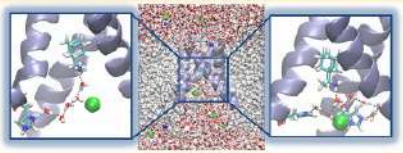
Paraskevi Gkeka,[†] Stelios Eleftheratos,[‡] Antonios Kolocouris,*[,‡] and Zoe Cournia*[,†]

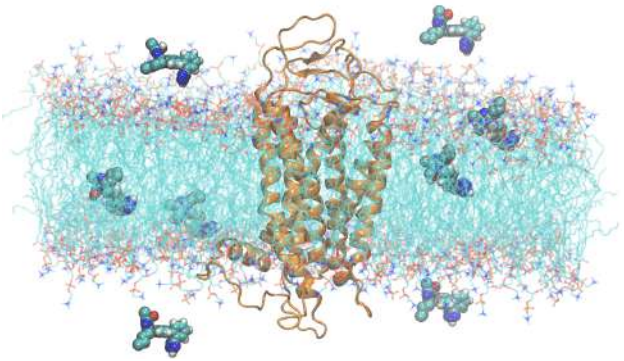
[†]Biomedical Research Foundation of the Academy of Athens, 4 Soranou Ephessiou, 11527 Athens, Greece

[‡]Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupolis-Zografou, 15771 Athens, Greece

Supporting Information

ABSTRACT: Aminoadamantane derivatives, such as amantadine and rimantadine, have been reported to block the M2 membrane protein of influenza A virus (A/M2TM), but their use has been discontinued due to reported resistance in humans. Understanding the mechanism of action of amantadine derivatives could assist the development of novel potent inhibitors that overcome A/M2TM resistance. Here, we use Free Energy Perturbation calculations coupled with





Biochimica et Biophysica Acta 1838 (2014) 1031–1046

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Insights into the molecular basis of action of the AT_1 antagonist losartan using a combined NMR spectroscopy and computational approach

Maria Zervou [a,*], Zoe Cournia [b], Constantinos Potamitis [a], George Patargias [b], Serdar Durdagi [a,1], Simona Golic Grdadolnik [c,d], Thomas Mavromoustakos [a,e]

[a] National Hellenic Research Foundation, Institute of Biology, Medicinal Chemistry & Biotechnology, Vas. Constantinou 48, 11635 Athens, Greece
[b] Biomedical Research Foundation of the Academy of Athens, 4, Soranou Efesiou, 11527 Athens, Greece
[c] Laboratory of Biomolecular Structure, National Institute of Chemistry, Hajdrihova 19, POB 30, SI-1115 Ljubljana, Slovenia
[d] EN-FIST Centre of Excellence, Dunajska 156, SI-1000 Ljubljana, Slovenia
[e] Chemistry Department of National Capodistrian University, Zographou, Athens 15784, Greece

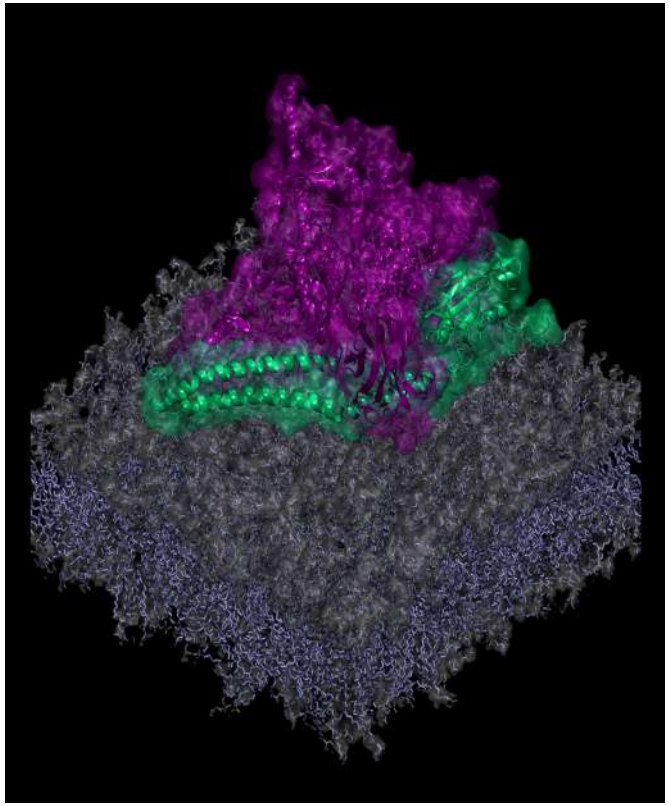
Through these publications was able to successfully apply for PRACE resources

PRACE-GR – ARIS: The Greek HPC System

Total: ~10 M core hours awarded (2014-2021)

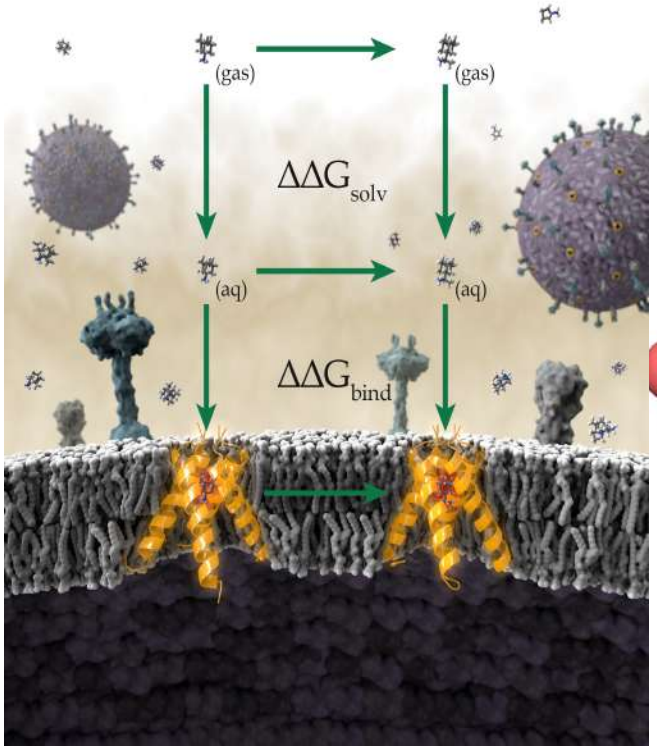
Protein-membrane interfaces in drug design

Peripheral Proteins



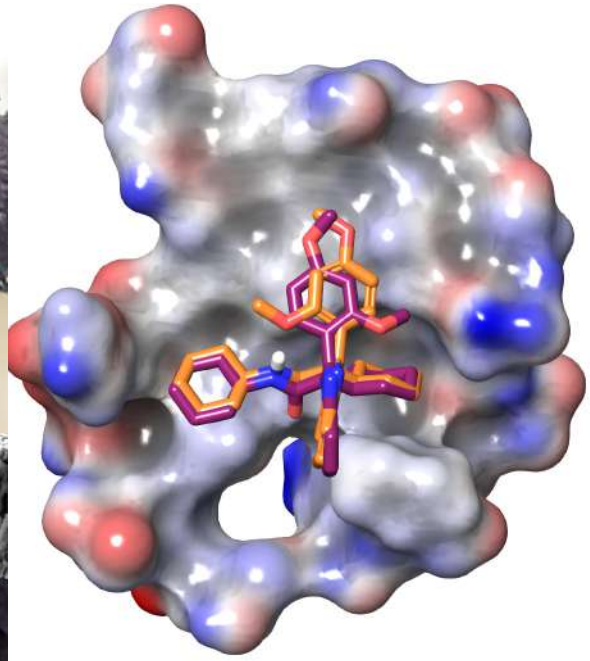
Leontiadou et al, Sci Rep, 2018
Gkeka et al, J Phys Chem B, 2015
Gkeka et al, PLOS Comp Biol, 2014

Ion Channels



Cournia et al, J Chem Inf Model, 2018
Gkeka et al, J Chem Inf Model, 2013
Ioannidis et al, J Chem Inf Model, 2016

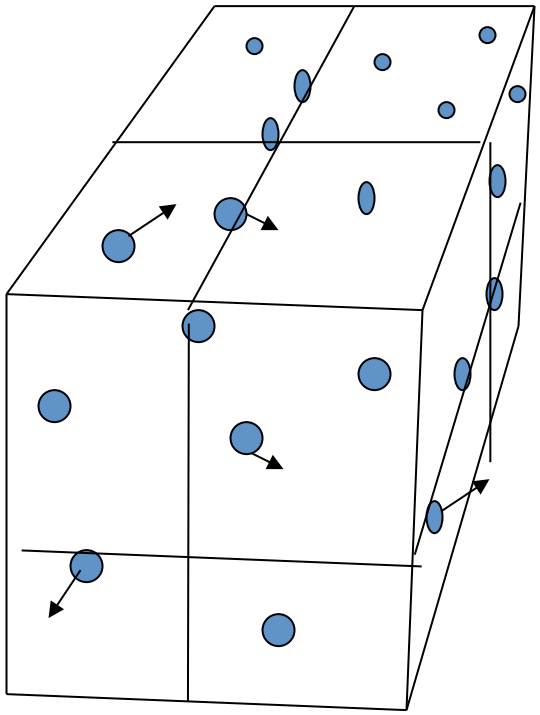
Drug Design

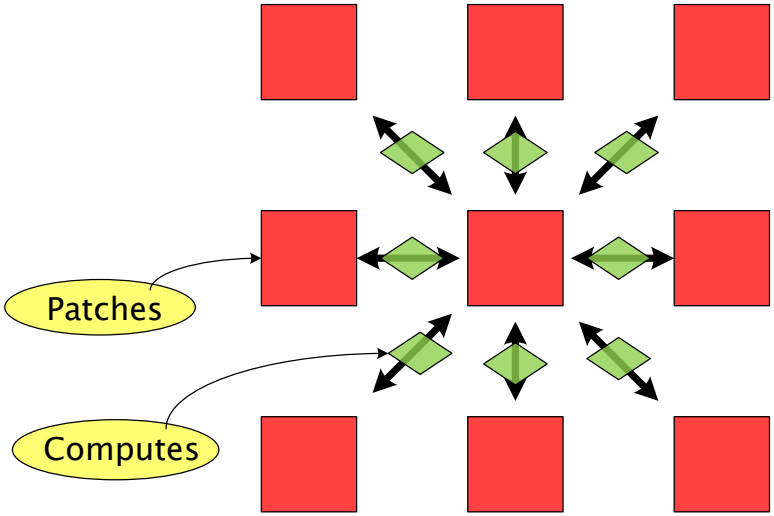


Athanasiou et al J Comput Aid Mol Des, 2018
Lionta et al, Curr Top Med Chem, 2014

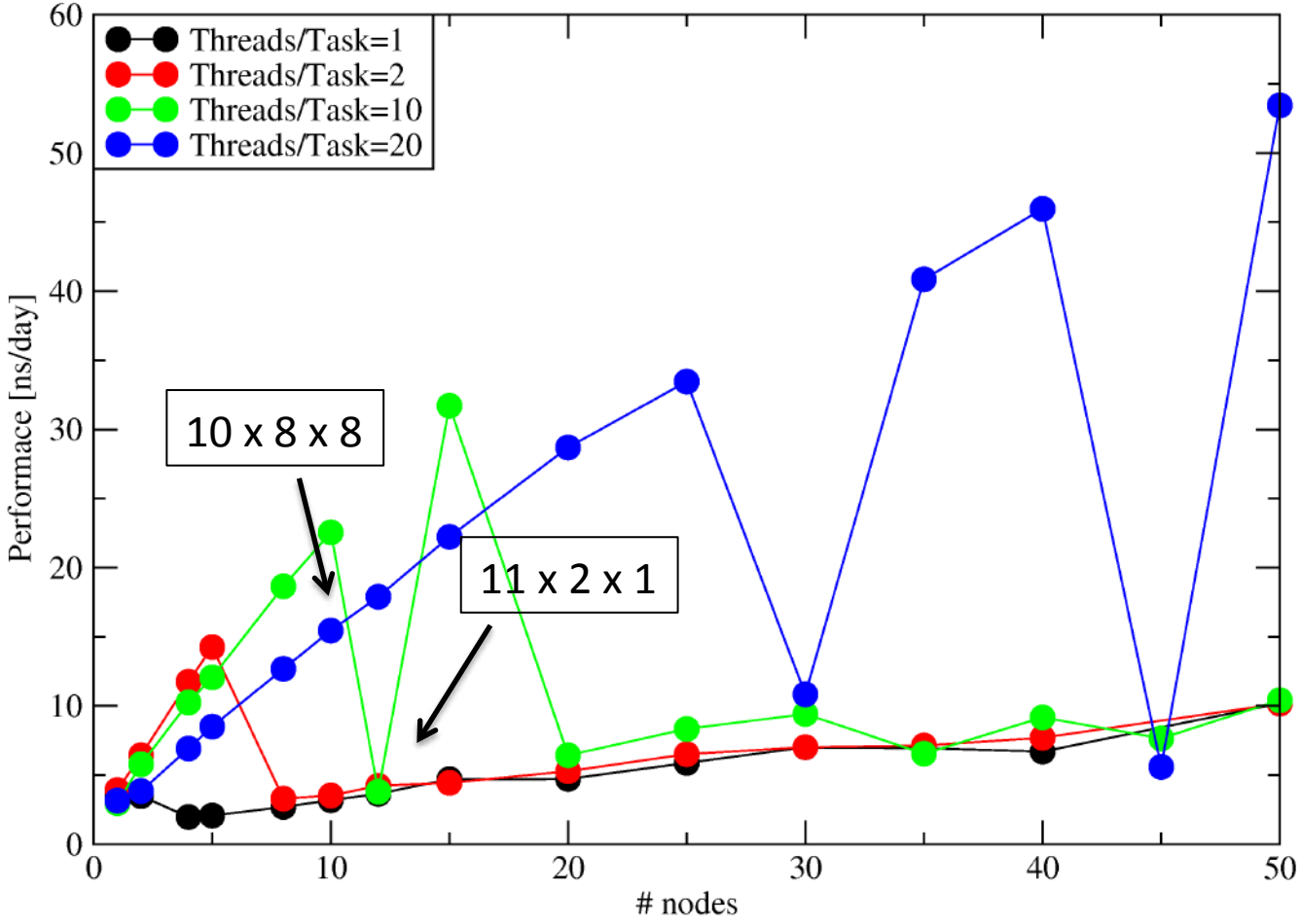
MD Simulator requirements

- **System size: ~400.000 atoms**
- Parallelization
- (getting an idea of the level of computation needed)
- Whole System is broken down into boxes (processing nodes)
- Each node handles the bonded interactions within a cutoff





GRNET HPC Support: Optimizing Performance

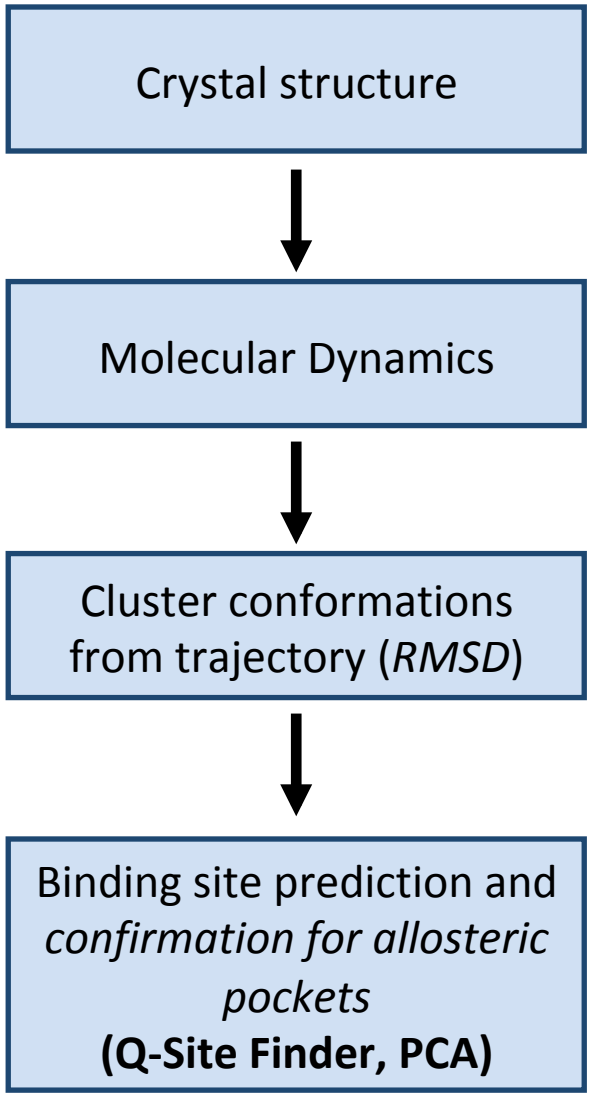


Dimitris Dellis
GRNET

PI3Kα
(400,000 atoms)

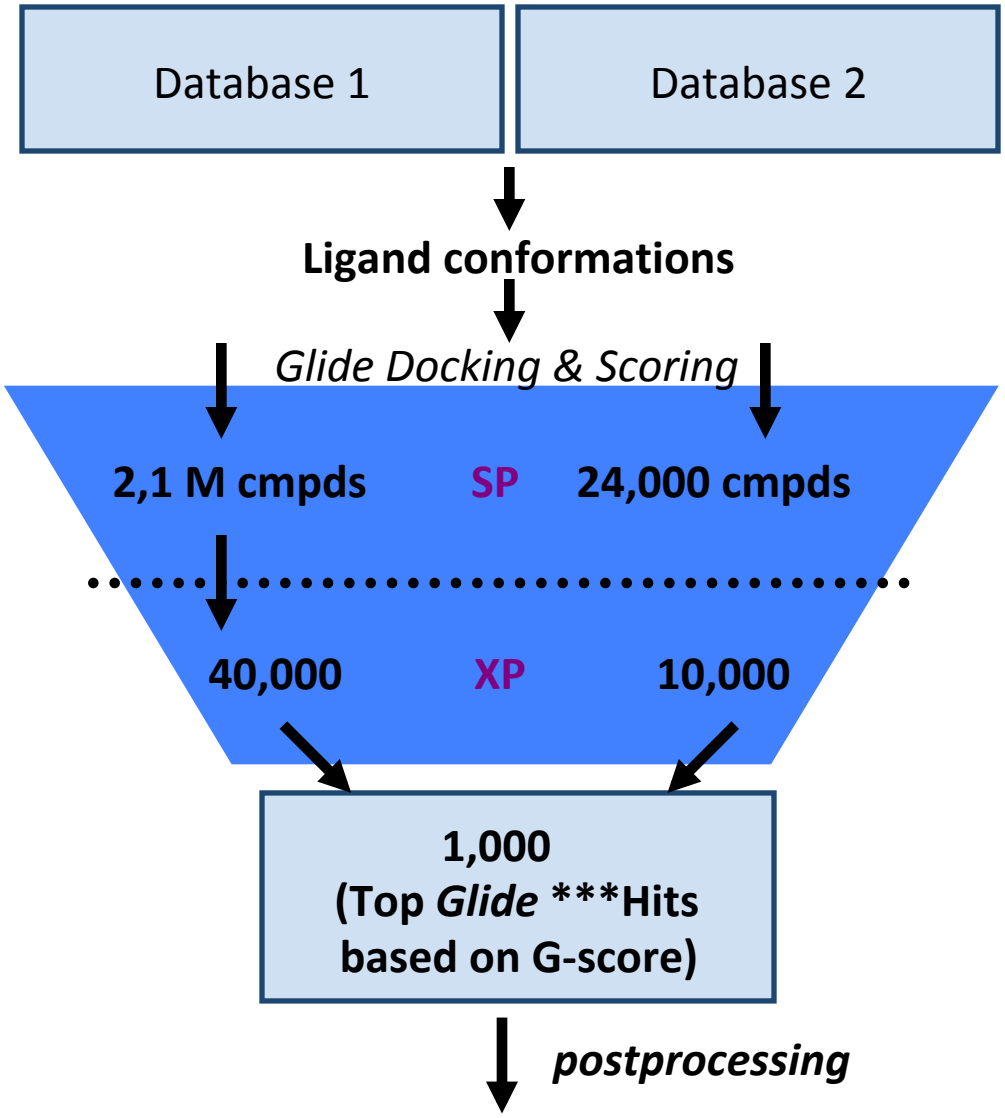
- **Both the communication and the box 3D decomposition** in cores has to be optimal in order to gain maximal performance.
- Decomposition 11 x 2 x 1 is **NOT optimal**
- Decomposition 10 x 8 x 8 is **optimal**

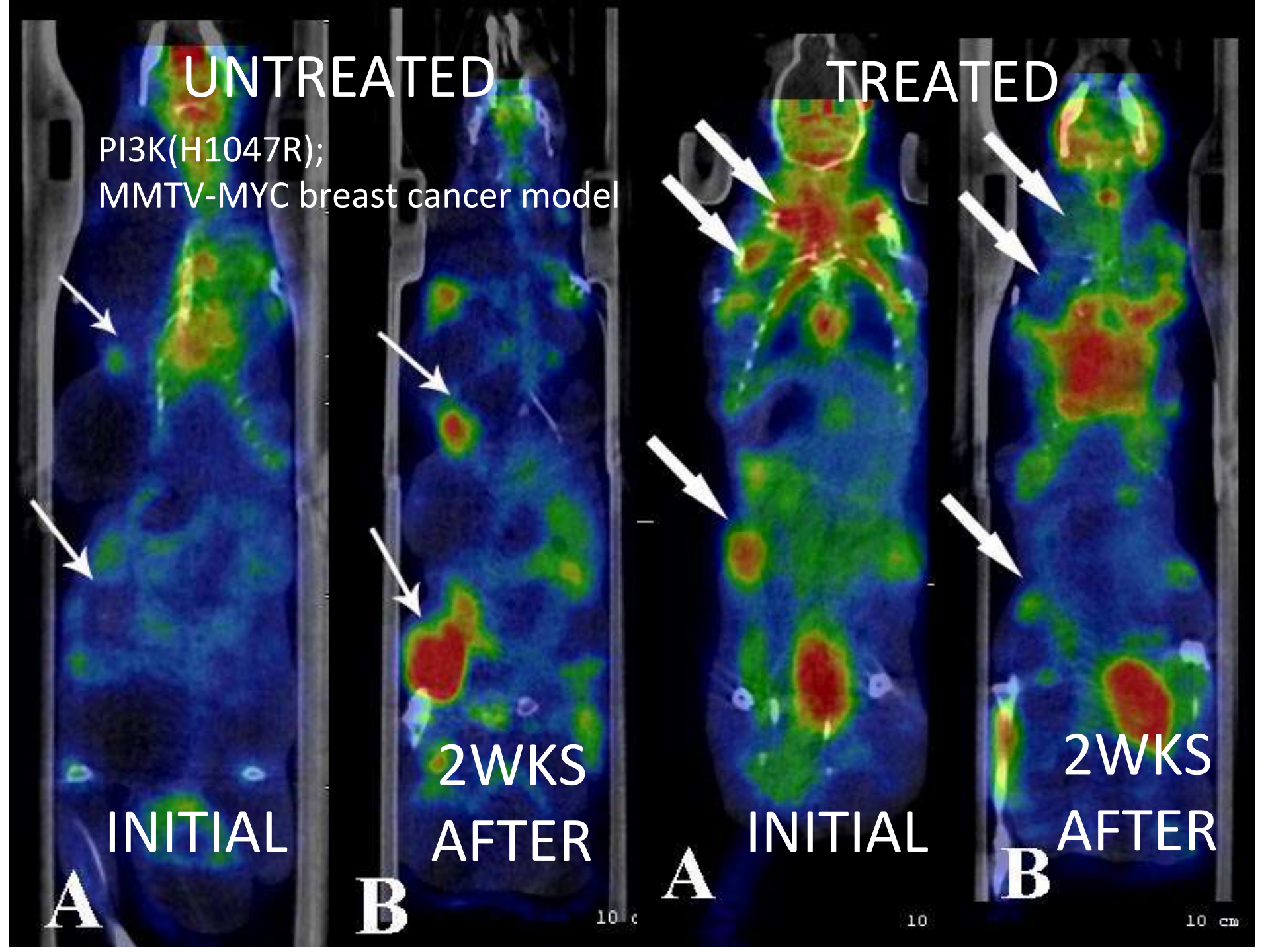
Binding site Prediction



Lionta et al, *Curr Top Med Chem* (2014)

Virtual Screening




UNTREATED
TREATED
PI3K(H1047R);
MMTV-MYC breast cancer model
INITIAL
2WKS AFTER
INITIAL
2WKS AFTER
A
B
A
B
10
10 cm

Intellectual Property

1) **Z. Cournia**, S Christoforidis, A Kapela, E Couladouros, A Efstratiadis, “Method of preparation and use of phosphoinositide 3-kinase inhibitors in treating cancer”. **PCT/EP2019/072648.**

2) **Z. Cournia**, S Christoforidis, A Kapela, E Couladouros, A Efstratiadis, “Novel allosteric phosphoinositide 3-kinase alpha inhibitors and applications thereof”. **German Patent Application No. 10 2020 202 356.5.**

3) D. Stellas, **Z. Cournia**, C. Tamvakopoulos, A. Klinakis & A. Efstratiadis. “Novel Compounds for use in treating or preventing cancerous diseases”. **US Patent 10,287,294. Application number EP 15 175 918.0**.

4) D. Stellas, **Z. Cournia**, C. Tamvakopoulos, A. Klinakis & A. Efstratiadis. “Compounds for use in treating or preventing cancerous diseases”. **International Patent Application number PCT/EP2015/050169.**

NOVARTIS
NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH

VRE for regional Interdisciplinary communities in Southeast Europe and the Eastern Mediterranean

Coordinator: GRNET

Oct 2015 – Sep 2018

Life Sciences - Scientific Community

Dr. Zoe Cournia

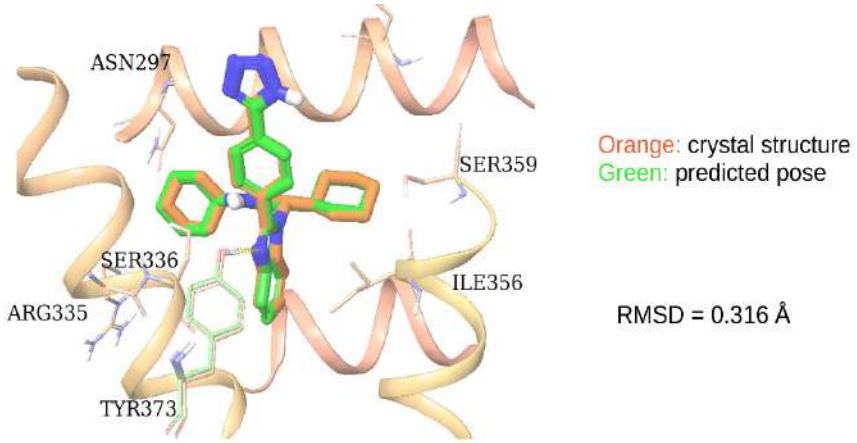
Life Sciences Scientific Community Leader

Biomedical Research Foundation, Academy of Athens

VI-SEEM Success Story: The D3R Project

Farnesoid X Receptor (FXR) – Computer-Aided Drug Design competition:
D3R challenge Grand Challenge 2 (Oct 2017 – Feb 2018)

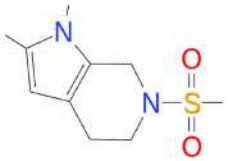
- **Worldwide drug design competition organized by University California, San Diego & Roche Pharmaceuticals**
- Goal: Predict blinded experimental data courtesy of Roche
- **D3R project was allocated 5,000 GPU card hours of VI-SEEM resources**

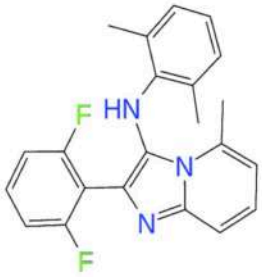


- C. Athanasiou, S. Vasilakaki, Z. Cournia (Biomedical Research Foundation Academy of Athens)
- D. Dellis (Greek Network of Research and Technology)
- W. Sherman (Silicon Therapeutics)

VI-SEEM Success Story: The D3R Project

- Ranked #1 out of 46 teams in this worldwide drug design competition

	Benzimidazoles	Sulfonamides	Spiros	Isoxazoles	Miscellaneous
	6-9, 13-14, 19-22, 24-32, 35-36	15-17	10-12	4, 23, 33	1-3, 5, 18, 34
Mean RMSD:	**0.84 Å**	**2.95 Å**	**3.45 Å**	**4.94 Å**	**5.57 Å**
Mean Rank:	**8**	**6**	**9**	**43**	**24**

- ✔ Known chemotype in crystal structures
- ✔ Docking, alignment, minimization worked really well
- ✔ Cross docking predicted unknown binding mode
- ✔ Cross docking predicted unknown binding mode
- ✔ Diversity in binding modes did not allow for accurate prediction
- ✔ Cross docking did not work

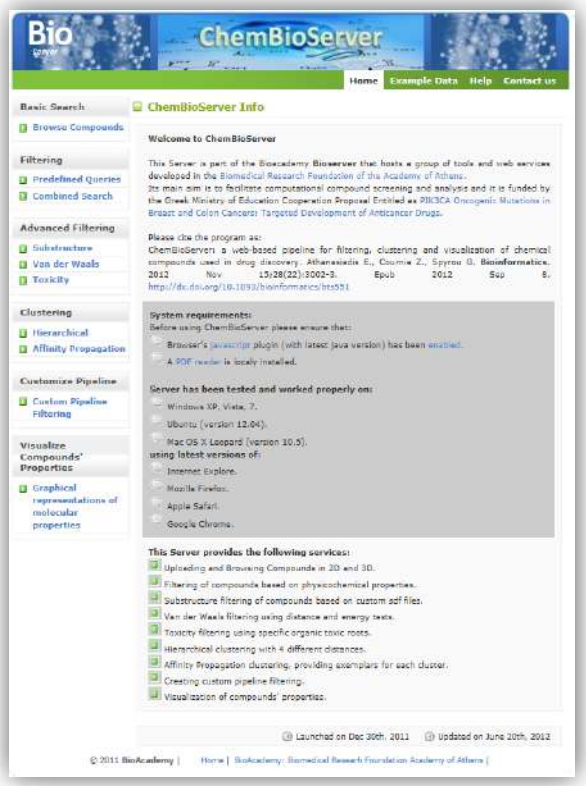
Athanasiou et al, JCAMD 2018

VI-SEEM Thematic Services

- ChemBioServer

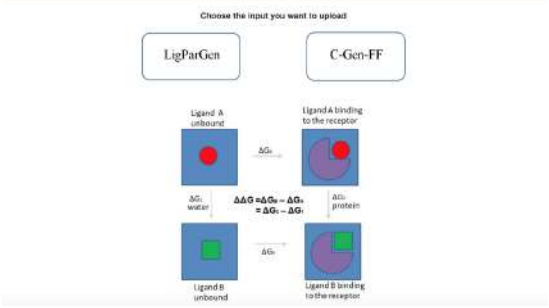
http://chembioserver.vi-seem.eu/

Service for filtering, clustering and visualization of chemical compounds used in drug discovery



- FEPrepare

http://feprepare.vi-seem.eu

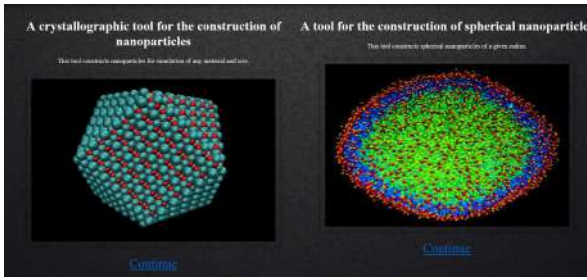


- Subtract

http://subtract.vi-seem.eu/

- Nano-Crystal

http://nanocrystal.vi-seem.eu/



- AFMM

http://afmm.vi-seem.eu/

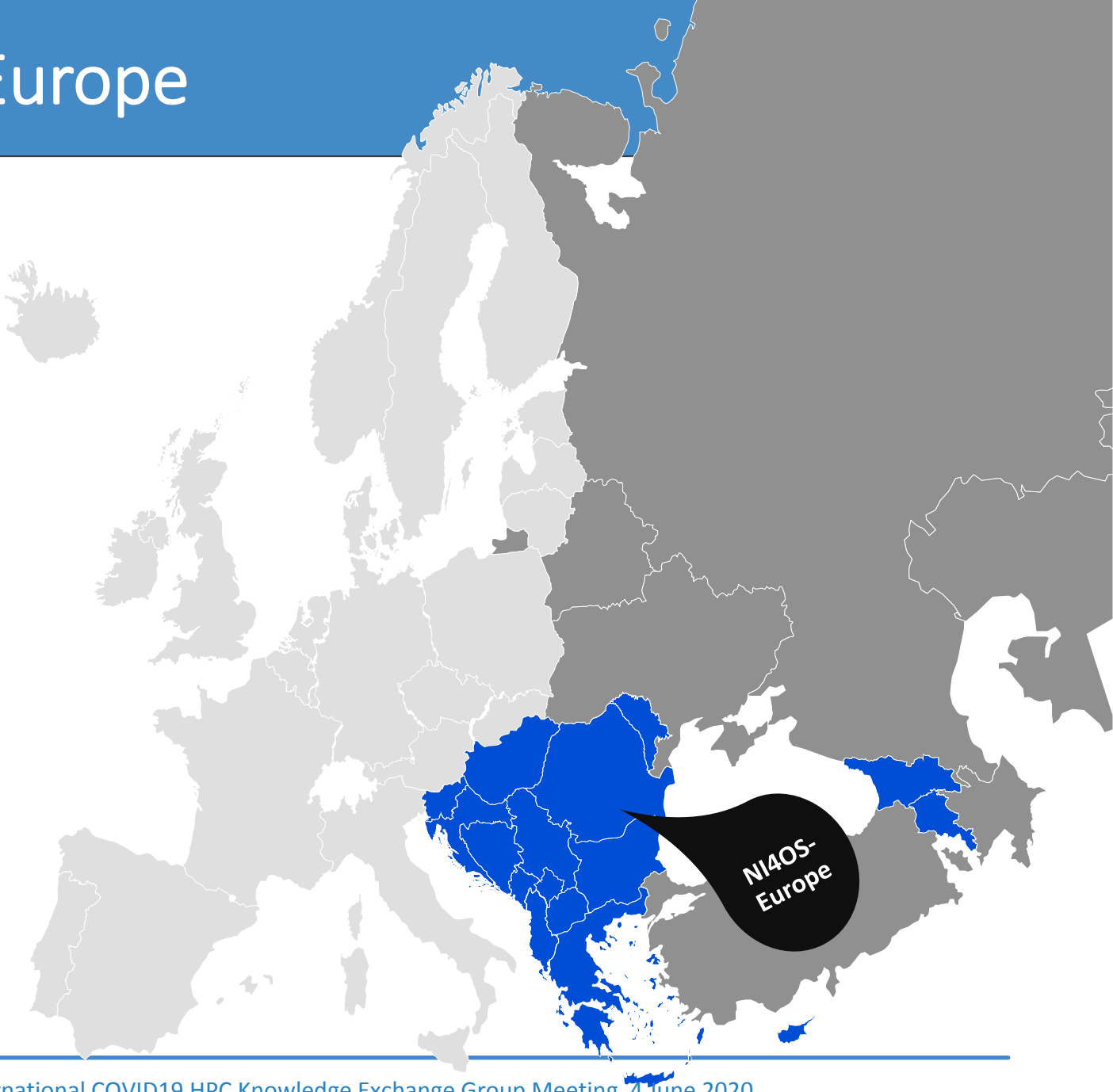
National Initiatives for Open Science in Europe

NI4OS-EU vs COVID-19

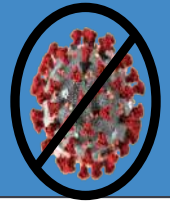
Zoe Cournia, BRFAA
Life Sciences Scientific Community Leader

NI4OS-Europe

Greece
Cyprus
Bulgaria
Croatia
Serbia
Slovenia
Hungary
Romania
Albania
Bosnia-Herzegovina
North Macedonia
Montenegro
Moldova
Armenia
Georgia



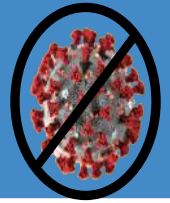
Credits: Federica Tanlongo – GARR
federica.tanlongo@garr.it - EOSC-Pillar



NI4OS-Europe Covid-19 Fast Access Channel

- **NI4OS-Europe takes action in the fight against COVID-19:**
  - NI4OS-Europe opens a fast track access channel to its
    - Generic services -computational (HPC, Cloud)
    - Data Analyzing tools
    - Storage services
    - Thematic Services related to covid-19
    - For scientific communities that perform extensive research to tackle the COVID-19.

- **APPLY and gain Fast Track Access to NI4OS-Europe resources:**
  - Are you a researcher, contributing in the fight against COVID-19?
  - Seize the opportunity and make use of NI4OS Fast Access Channel!
  - Contact us at: ni4os-europe-covid19@ni4os-europe.eu



NI4OS-Europe Covid-19 Fast Access Channel

- **The initiation procedure to the fast access channel is as follows:**
  - Contact NI4OS-Europe fast access channel at ni4os-europe-covid19@ni4os-europe.eu and express your need by briefly describing:
    - Area of research,
    - Estimated overall computational load and usage pattern in the near future,
    - Execution environment (programming language, libraries),
    - Parallelization requirements, if any,
    - Data exchange, etc.
  - Needs will be matched against the available resources and you we will responded soon.
  - An online meeting might be arranged so that the needs of the project are discussed.
  - You will be provided details on how to access the resources.

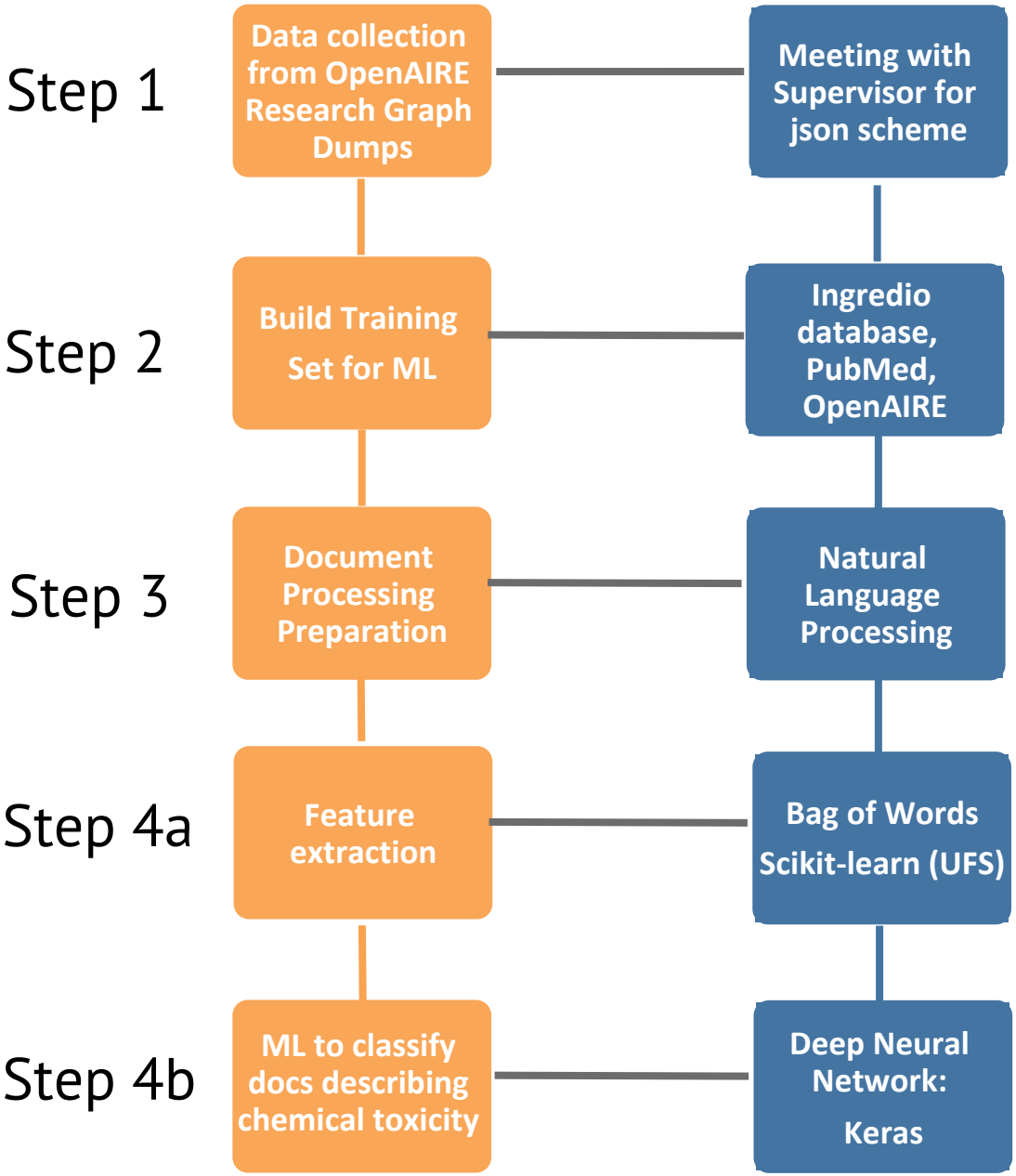
  - **CPUs, GPUs, Phi-cards available.**

Computational Resources Available

- **Computational resources have already been allocated to:**
  - The Bioinformatics European Research Era Chair and the Bioinformatics Group at the Cyprus Institute of Neurology and Genetics.
  - **“Network-based multiomics integration boosts drug respurposing against COVID-19.”**

Enhancing the food & cosmetics OpenAIRE Research Graph for consumer health

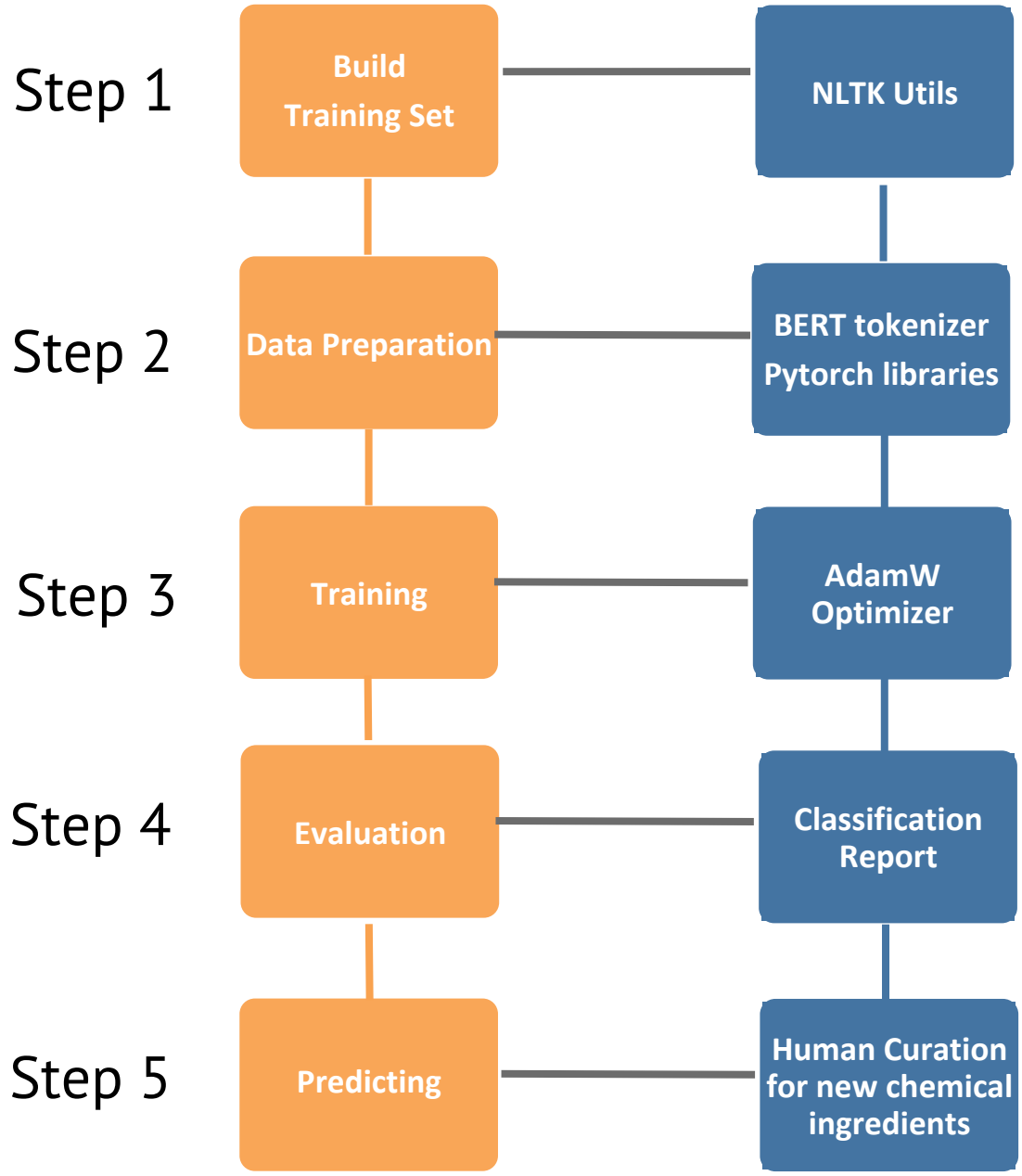
Workflow of the Project



Objective 1

Develop text mining and Machine Learning algorithms to extract OpenAIRE data linking chemical ingredients of food &cosmetics to potential health hazards

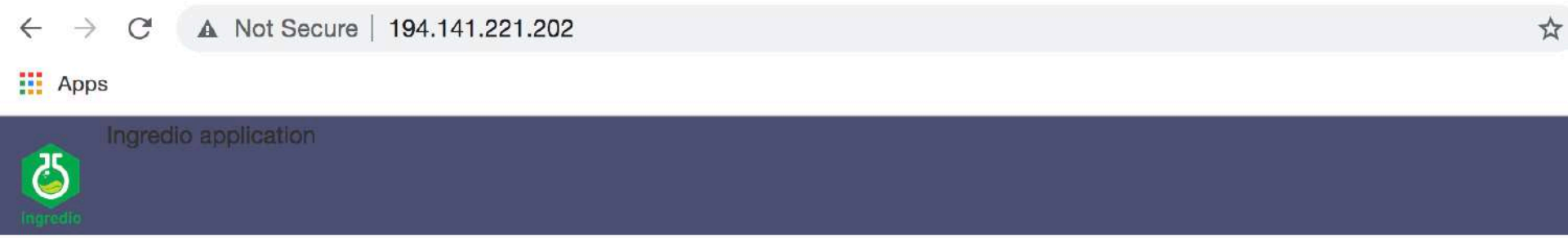
Workflow of the Project



Objective 2

Identifying new chemical ingredients from the OpenAIRE data to enrich the OpenAIRE research graph & the Ingredio database

Onboarding to EOSC (NI4OS-Europe)

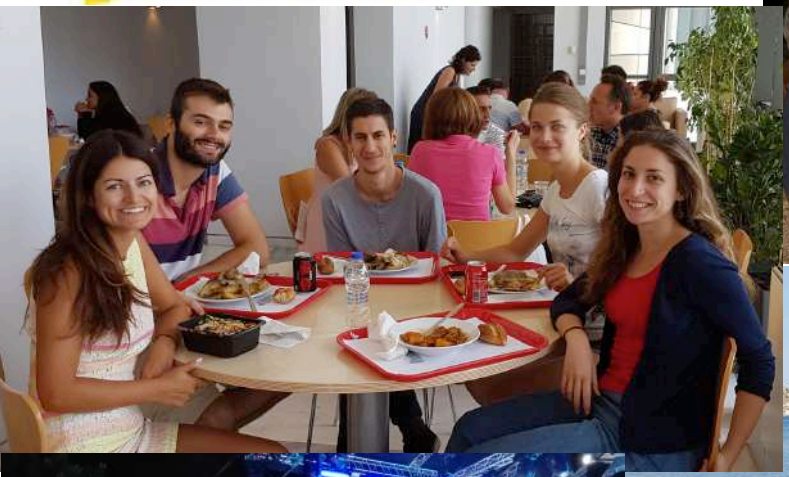


- ✓ A dedicated server was provided by NI4OS-Europe (BAS - Bulgaria) with 8 NVIDIA Tesla M2090 on 24.1.2021
- ✓ A web-server was developed and uploaded in https://ingredio.ni4os.eu/
- ✓ Web-server is onboarded in NI4OS-Europe

Coordinator GRNET 2016: I Liabotis
Coordinator GRNET 2018: A Sotiropoulos
Supervisors: D Dellis (GRNET), Z Cournia (BRFAA)

2016:
Juan Zamora (Imperial Coll., UK)
Samanta Makurat (Gdansk U, PL)

2018:
Pedro Santos (Coimbra U, PT)
Petteri Vannika (Turku U, FL)



Infrastructure on High Performance Computing

Pan-European Research

HPC Europa

Coordinator GRNET : E Athanasaki

Supervisors: Z Cournia (BRFAA) / D Dellis (GRNET)

Leandro Battini
University of Buenos Aires
Argentina

15.11.2018 – 28.2.2019

Optimization of antivirals against Chikungunya virus using Free Energy Perturbation method

Phaedon Brotzakis
ETH Zurich
Switzerland

8.1.2019 – 20.3.2019

Conformational studies of wild-type and mutated K-Ras binding to a membrane

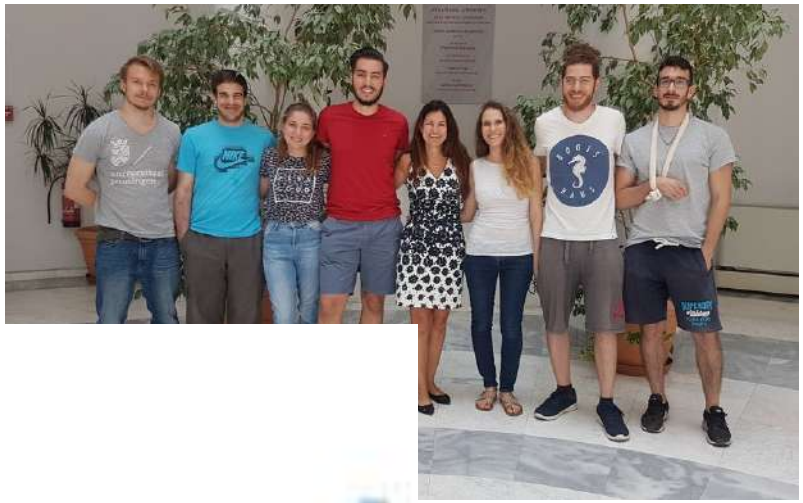
Michail Paparoudakis
University of Ediburgh
UK

1.2.2019 – 20.4.2019

Investigating predictive models for the discovery of new c-Myc inhibitors

Project Team & Thank you!

BRFAA
Cournia lab (MD, drug design, cells)
Dr. Evi Gkeka
Dr. Hari Leontiadou
Ioannis Galdadas, Christina Athanasiou



Efstratia
Dr. Ersi
Dr. Dimi

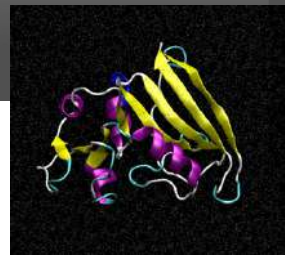
NCSR D
Coulado
Anna Ka
Maria Ou

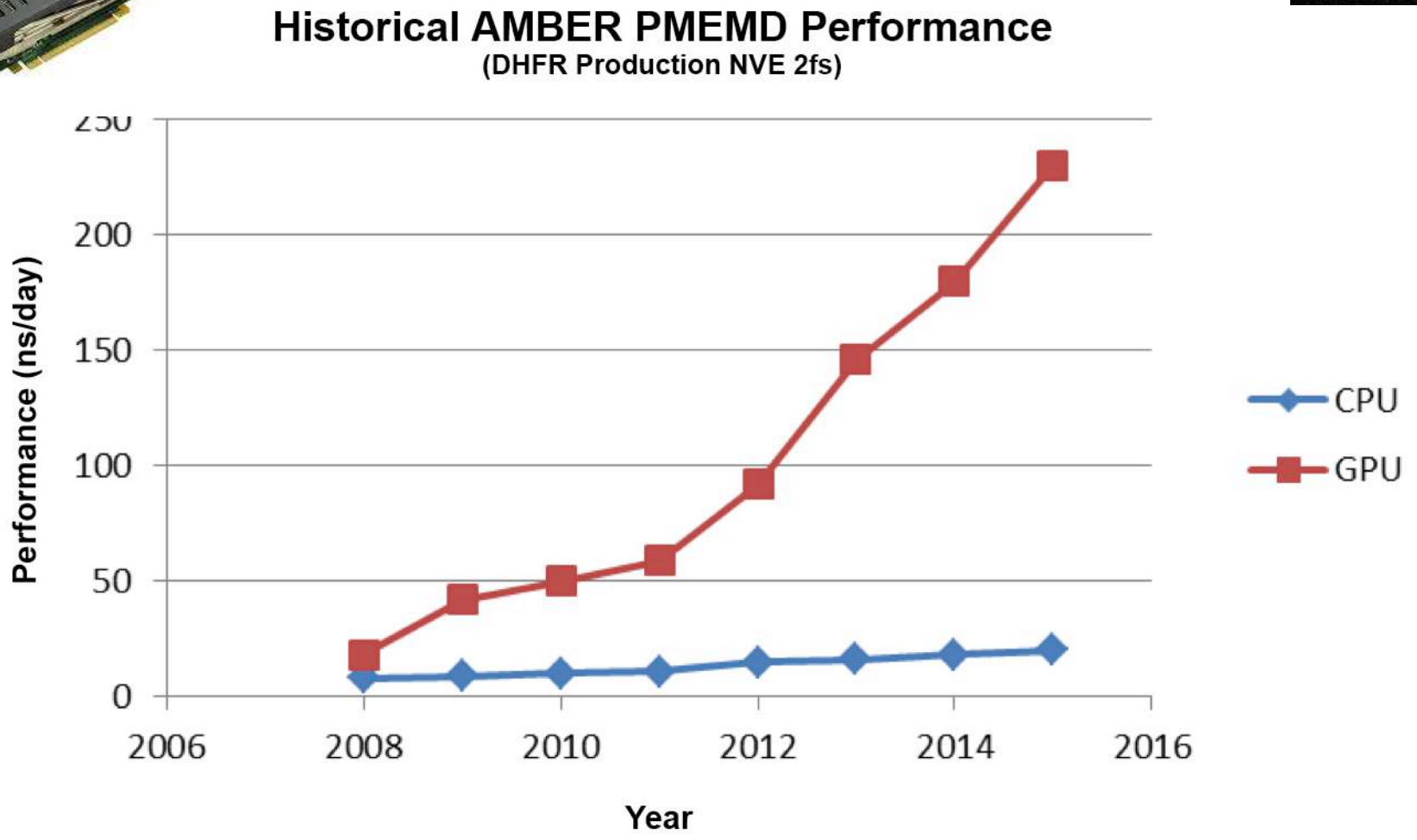
Universi
Agianiar
Dr. Maria

University of Ioannina
Christoforidis lab (cell-free assays)
Alexandra Papafotika
Dr. Vasiliki Lazani

BACKUP SLIDES

The new era: GPU acceleration





Credit: Professor Ross Walker, UCSD Supercomputing Center, AMBER developer